

Severe hypocalcemia following denosumab treatment in a patient with secondary osteoporosis associated with primary sclerosing cholangitis

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Abstract. Primary sclerosing cholangitis (PSC) has been known as a cause of secondary osteoporosis, which often requires medication. Herein, we give the first report of a case of a 38-year-old man with fatigue and paralysis in both upper limbs who had been treated with denosumab for secondary osteoporosis associated with PSC. Since bisphosphonate (alendronate) was ineffective in our patient, the treatment was changed from alendronate to denosumab. Despite replacements with calcium and active vitamin D (alfacalcidol; 1-hydroxycholecalciferol), he developed severe hypocalcemia (albumin-adjusted serum calcium: 5.2 mg/dL) 2 weeks after the second administration of denosumab, which required immediate correction. After that, the corrected serum calcium levels were controlled within the normal range with 0.75 µg of eldcalcitol (1 α ,25-dihydroxy-2 β -(3-hydroxypropyloxy)vitamin D3) and increased doses of calcium (1,500 mg daily) and phosphate (900 mg daily) without denosumab. Even though denosumab treatment had been terminated, the T score of the lumbar spine improved from -4.4 to -2.6 by 1 year after the second administration, possibly due to the amelioration of osteomalacia through the treatment with eldcalcitol and the higher doses of calcium and phosphate. This report indicates that denosumab can cause severe hypocalcemia in patients with osteoporosis associated with chronic diseases of the hepatobiliary system including PSC, in turn suggesting that the possibility of vitamin D deficiency or osteomalacia should be considered before administering treatments and that serum calcium levels should be closely monitored to detect life-threatening hypocalcemia in patients who have high risk factors for hypocalcemia.

Key words: Denosumab, Hypocalcemia, Primary sclerosing cholangitis (PSC), Osteoporosis

PRIMARY SCLEROSING CHOLANGITIS (PSC), a chronic inflammatory disease of intra- and extrahepatic bile ducts, has been reported to be accompanied by osteoporosis in 15% of patients [1, 2]. Due to the disturbances in vitamin D metabolism, the risk of osteoporosis increases in patients with chronic diseases of the hepatobiliary system, including cirrhosis, primary biliary cirrhosis (PBC) or PSC [3]. Therefore, those patients require calcium and active vitamin D supplementation [3, 4] and medications with bisphosphonate or denosumab. No reports so far have shown that denosumab causes severe hypocalcemia in patients with cholestatic diseases including PBC and PSC. We herein report the first case of severe hypocalcemia by denosumab treatment in a patient with secondary osteoporosis associated with PSC.

Submitted Oct. 30, 2018 as EJ18-0470; Accepted Jan. 7, 2019 as EJ18-0545
Released online in J-STAGE as advance publication Feb. 2, 2019
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Case Report

A 38-year-old man was diagnosed with PSC at age 17, and was initially treated with 5 mg of prednisolone daily for 5 years. Seventeen years after the diagnosis of PSC, he was first evaluated for bone mineral density (BMD) and diagnosed with secondary osteoporosis possibly due to PSC and previous glucocorticoid treatment. Then, he started with 35 mg of alendronate daily and 1 µg of active vitamin D (alfacalcidol; 1-hydroxycholecalciferol) daily, which was 4 years ago. Since this treatment did not improve his lumbar spine BMD (from 0.402 g/cm² to 0.361 g/cm² over 3 years), it was changed to denosumab. The patient had the first injection with 60 mg of denosumab 6 months before admission when the total bilirubin level was 9.3 mg/dL. Although he experienced no adverse events during the 6 months after the first administration, he complained of fatigue and paralysis in both upper limbs 2 weeks after the second administration of denosumab. Because the symptoms were getting worse, he had an evaluation at our hospital. The physical examination at the time of admission revealed that he was posi-

Table 1 Biochemical data of the patient before and after admission

| Biochemical parameter | At the second administration of denosumab | Time of the admission | 1 year after discharge | Normal range |
|------------------------------------|---|-----------------------|------------------------|--------------|
| Calcium (mg/dL) | 8.7 | 4.8 | 8.4 | 8.7–10.3 |
| Corrected calcium (mg/dL) | 9.1 | 5.2 | 9.0 | 8.7–10.3 |
| Phosphate (mg/dL) | 2.1 | 1.3 | 3.5 | 2.5–4.7 |
| Magnesium (mg/dL) | 2.3 | 1.9 | 1.9 | 1.9–2.5 |
| Alkaline phosphatase (U/L) | 2,970 | 2,350 | 2,116 | 115–359 |
| Albumin (g/dL) | 3.6 | 3.6 | 3.4 | 4.0–5.0 |
| 25(OH)D (ng/mL) | <4.0 | <4.0 | <4.0 | — |
| Creatinine (mg/dL) | 0.36 | 0.36 | 0.38 | 0.60–1.10 |
| eGFR (mL/min/1.73 m ²) | 212 | 212.1 | 198.4 | — |
| Total bilirubin (mg/dL) | 14.2 | 17.2 | 6.5 | 0.3–1.2 |
| Direct bilirubin | 10.0 | 12.6 | 4.3 | 0–0.2 |
| Serum NTx (nmol BCE/L) | 41.2 | 8.6 | N/A | — |
| Serum BAP (µg/L) | 72.0 | 227.0 | 113 | 3.7–20.9 |
| Intact PTH (pg/mL) | 277.5 | 429.8 | 142.2 | 10.3–65.9 |

Corrected calcium: serum calcium + (4-serum albumin)

25(OH)D, 25-hydroxyvitamin D; eGFR, estimated glomerular filtration rate; NTx, N-terminal telopeptide of type I collagen; BCE, bone collagen equivalents; BAP, bone-specific alkaline phosphatase; PTH, parathyroid hormone

N/A: not available

tive for Chvostek's sign. The following measurements were obtained: his height and weight were 170 cm and 43 kg (body mass index [BMI]: 13 kg/m²), respectively. His vital signs were as follows: blood pressure, 92/59 mmHg; heart rate, 69 bpm; respiratory rate, 18 bpm on room air; and body temperature, 36.9°C.

The initial laboratory data are shown in Table 1. The serum calcium level was normal at the second administration of denosumab under the replacement with 1,500 mg of calcium daily, 200 mg of phosphate daily and 1 µg of alfacalcidol daily. The level of total bilirubin (14.2 mg/dL) was higher than that (9.3 mg/dL) at the first administration of denosumab. The electrocardiogram showed a prolonged QTc. Abdominal computed tomography revealed wall thickening of the common bile duct and the hilar bile duct; strictures of intrahepatic bile duct, which were consistent with findings of PSC; and intrahepatic stones. He was diagnosed with severe hypocalcemia (Common Terminology Criteria for Adverse Events v4.0: grade 4) induced by denosumab and was admitted to the intensive care unit (ICU) for monitoring of his general condition and correcting his serum calcium and phosphate levels.

After starting intravenous calcium and phosphate replacement, the patient's serum calcium levels gradually improved (Fig. 1). Based on the improvement of his serum calcium levels to 9.0 mg/dL, the patient was dis-

charged from the ICU 4 days later. Since alfacalcidol was ineffective possibly due to disturbances of 25-hydroxylation by high levels of bilirubin, it was changed to eldecalcitol (1α,25-dihydroxy-2β-(3-hydroxypropyloxy) vitamin D3). Additionally, to reduce the cholestasis, the patient had a drainage tube placed in the bile duct. Since serum calcium levels were then maintained within the normal range with 5,000 mg of oral calcium daily, 1,500 mg of phosphate daily and 0.75 µg of eldecalcitol daily, he was discharged from the hospital 1 month later. Then, corrected serum calcium levels have been controlled within the normal range with 1,500 mg of oral calcium daily, 900 mg of phosphate daily and 0.75 µg of eldecalcitol daily (Table 1). The T score of BMD was -4.6 at the lumbar spine before the first administration of denosumab. Even though denosumab treatment was terminated, the score reached -2.6 by 1 year after the second administration (Table 2). In addition, the levels of serum type I collagen cross-linked N-telopeptide (NTx), a peptide that reflects the state of bone resorption, decreased from 41.2 to 8.6 nmol bone collagen equivalents/L by the second administration of denosumab (Table 1).

Discussion

Osteoporosis is a common disease characterized by a systemic impairment of bone mass and microarchitec-

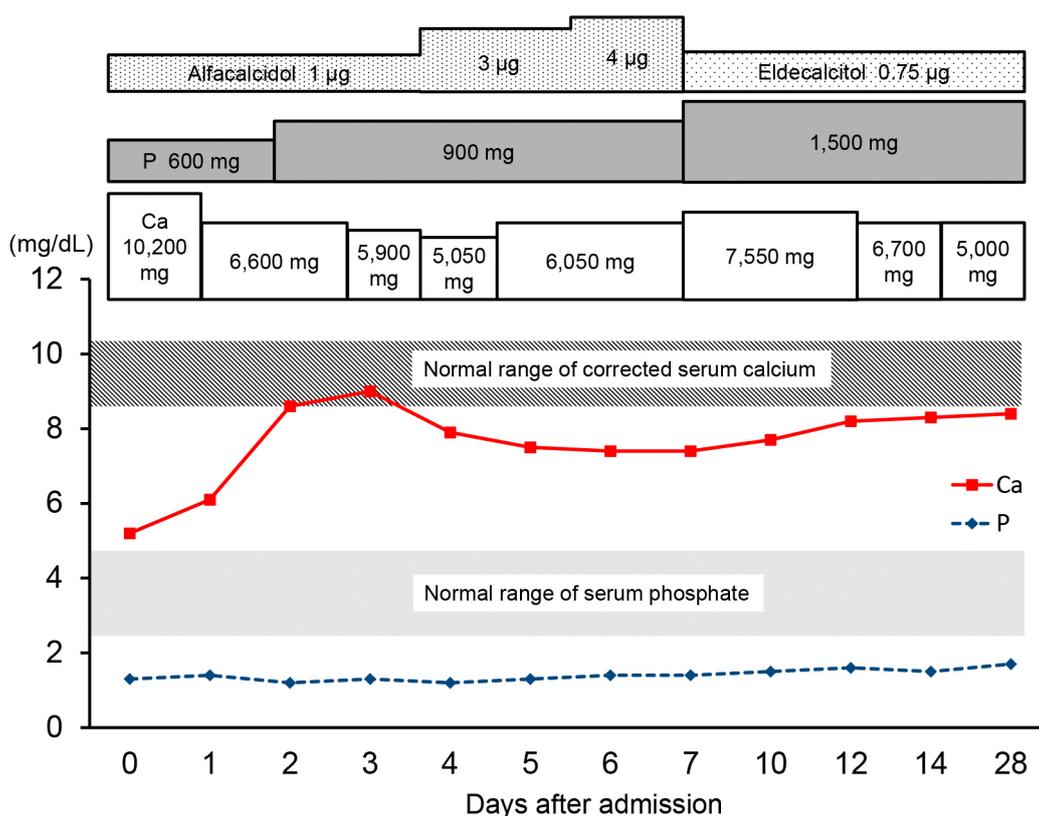


Fig. 1 Changes of corrected serum calcium and phosphate levels after admission

Table 2 Changes of T score and BMD

| Biochemical parameter | Before the first administration of denosumab | Before the second administration of denosumab | 1 year after discharge |
|--|--|---|------------------------|
| T score of the lumbar spine | -4.6 | -4.4 | -2.6 |
| T score of the hip | -5.9 | -5.9 | -5.1 |
| BMD of the lumbar spine (g/cm ²) | 0.361 | 0.396 | 0.655 |
| BMD of the hip (g/cm ²) | 0.171 | 0.174 | 0.276 |

BMD, bone mineral density

ture, resulting in fragility fractures [5]. Primary osteoporosis develops from age-related bone loss and idiopathic disease in men [6]. The more common etiologies of secondary osteoporosis include glucocorticoid excess, excessive alcohol intake and hypogonadism [7]. The less common etiologies of secondary osteoporosis include low BMI, thyrotoxicosis, primary hyperthyroidism, and chronic kidney or liver diseases (hepatic osteoporosis) [8]. Among patients with secondary osteoporosis, excess glucocorticoid is known to cause BMD loss and fractures. However, many patients receiving glucocorticoid treatment are not appropriately managed [9]. Although the patient in this report had taken 5 mg of prednisolone daily for 5 years, he did not receive any treatments for osteoporosis.

Hepatic disease is also known as a cause of secondary osteoporosis, but the pathogenesis remains unclear. Several possibilities are suggested as the mechanism of the pathogenesis of secondary osteoporosis in PSC. First, cholestasis prevents the absorption of vitamin D, which can cause significant bone loss in patients with PSC [2], and increases the levels of bilirubin, which have been shown to inhibit osteoblast function *in vitro* [10]. Second, interleukin (IL)-1 β and tumor necrosis factor (TNF)- α elevated by hepatic inflammation can activate osteoclasts [3]. Several studies have suggested that inflammatory cytokines including IL-1 β and TNF- α cause bone loss by direct or indirect effects with complicated mechanisms [11-14]. Third, low serum IGF-1 levels can play a role in bone mass loss in chronic liver

disease. BMD in the lumbar spine was positively correlated with serum IGF-1 levels, and serum IGF-1 concentrations in the patients with osteoporosis were lower than those in the patients without osteoporosis [15]. Although IGF-1 concentration was not measured in this case, low levels of IGF-1 could have been involved in the pathogenesis. Due to the high levels of total bilirubin occurring over 10 years in our patient, cholestasis may have been involved in the development and progression of osteoporosis. After admission, the patient had a drainage tube placed in the bile duct for reduction of cholestasis, which was followed by the improvement of total bilirubin levels from 17.2 to 12.8 mg/dL (normal range: 0.3–1.2 mg/dL). One year later, the total bilirubin level reached 6.5 mg/dL. In addition to the effect of denosumab, the decrease of the total bilirubin level may have in turn decreased the inhibition of osteoblast function, resulting in the improvement of the patient's lumbar spine BMD (from 0.361 to 0.655 g/cm²). Since the improved levels of BMD in lumbar spine and hip were still low, high risk of fracture should be a concern in the future.

Osteomalacia is a disease characterized by impaired mineralization of bone matrix [16, 17]. Based on the fact that alendronate has been shown to have no effects on mineralization [18], bisphosphonates are thought to be ineffective for the improvement of BMD in patients with osteomalacia. The levels of intact PTH levels were high even with the normal calcium levels at the second administration of denosumab, suggesting ineffectiveness of alfacalcidol. In addition, given that the patient had hypophosphatemia, he may also have had osteomalacia. It was reported that normalization of mineral ion homeostasis by the test diet (high calcium, high phosphate) prevented the development of osteomalacia in vitamin D receptor-ablated mice [19]. Therefore, replacements with higher doses of calcium and phosphate after the admission could have contributed to the amelioration of osteomalacia in this patient, which was another reason for the improvement of lumbar spine BMD after the second administration of denosumab. Regarding the improvement of lumbar spine BMD in this patient, it was also important to change the active vitamin D treatment from alfacalcidol to eldcalcitol, because the higher total bilirubin level could prevent 25-hydroxylation in the liver and the absorption of alfacalcidol in the intestine. Although there was no improvement of the T score of the lumbar spine after the first administration of denosumab, it increased after replacing alfacalcidol with eldcalcitol and administering the higher doses of calcium and phosphate despite the termination of denosumab. Taken together, eldcalcitol could improve osteomalacia, but not osteoporosis itself.

Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor- κ B ligand (RANKL), a cytokine that is essential for differentiation and activation of osteoclasts. It has been shown to increase BMD, reduce bone resorption and decrease fracture risk in postmenopausal women with osteoporosis [20]. ADAMO (a multicenter, randomized, double-blind, placebo-controlled Study to Compare the Efficacy and Safety of Denosumab Ab *Versus* Placebo in Males With Osteoporosis) is a Phase 3 trial for the use of denosumab to treat men with osteoporosis [21]. In this trial, the increase of lumbar spine BMD was 5.7% in the denosumab group and 0.9% in the placebo group over 12 months [21]. Although bisphosphonate is the most common medication for osteoporosis, it has been reported that denosumab was associated with increased BMD even in bisphosphonate-unresponsive cases [22]. Since alendronate was ineffective in our patient, the treatment was changed from alendronate to denosumab. Hypocalcemia has been reported in 0.4% (2/475) of patients with osteoporosis in a phase 3 clinical trial in Japan [23] and in 0% (0/3,886) of patients in the phase 3 randomized FREEDOM trial [20]. There were no reported cases of severe hypocalcemia in either study. In addition, there were no reports of severe hypocalcemia among patients with PSC treated with denosumab. Our patient developed severe hypocalcemia after the second administration of denosumab, despite replacements with calcium, phosphate and alfacalcidol. The total bilirubin level at the second administration (14.2 mg/dL) was much higher than at the first (9.3 mg/dL). It is possible that the higher bilirubin level contributed to the development of severe hypocalcemia after the second administration *via* the impaired 25-hydroxylation in the liver and intestinal malabsorption of alfacalcidol. Therefore, increased levels of bilirubin may be associated with severe hypocalcemia in denosumab treatment. If the patient had been treated with the active vitamin D eldcalcitol from the beginning, he might not have required such a high dose replacement of calcium and phosphate and not have developed severe hypocalcemia. Considering the possibility of impaired 25-hydroxylation of vitamin D in severe cholestatic conditions, it is necessary to select the appropriate type of active vitamin D. Although it has been reported that eldcalcitol increases BMD more strongly than alfacalcidol [24], the safety of eldcalcitol use in patients with severe liver dysfunction has not been established. Therefore, close monitoring of liver function is required in this patient.

In conclusion, denosumab can cause severe hypocalcemia in patients with osteoporosis associated with cholestatic diseases including PSC. It is important to consider the possibility of vitamin D deficiency or osteo-

malacia in chronic diseases of the hepatobiliary system including PSC, and to treat them by sufficient replacements with calcium, phosphate and active vitamin D before treatment with bisphosphonates or denosumab. In addition, it is important to closely monitor the levels of serum calcium and bilirubin after the initiation of denosumab treatment, especially in patients who have high

risk factors for hypocalcemia.

Disclosure

The authors state that they have no Conflicts of Interest in this paper.

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